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SEP 28 2001

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204
Telephone Number: (202) 205-4168

To Whom It May Concern:

Please consider the following information as notification of a dietary ingredient:

1. Manufacturer's Name and Address:

InterHealth Nutraceuticals, Inc.
5451 Industrial Way
Benicia CA 94510

2. Name of Dietary Ingredient:

trans-Resveratrol

3. Description of the Dietary Supplement:

- a. *Polygonum cuspidatum* root extract (trade name Protykin[®]) providing standardized levels (50%) of *trans*-resveratrol.
- b. For use as a dietary supplement in capsule, tablet, powder or liquid form.
- c. The recommended dosage as a dietary supplement is 0.5 – 4 milligrams *trans*-resveratrol per day.
- d. Recommended for the general healthy population over the age of 18. Not recommended for pregnant or nursing women. A statement referencing this will be disclosed on the label as a disclaimer.

4. History or Evidence of Safety:

This dietary supplement has been present in the food supply as an article in food and can reasonably be expected to be safe as follows:

- a. *Polygonum cuspidatum* is a traditional Chinese herb known as Hu-chang (pronounced "who-jun") and more commonly as knotweed. The essence and flavor of the root is sour, bitter and mildly pungent with "cold" Chinese medicinal properties. According to the *Oriental Materia Medica*, traditional uses of the root are to clear up "heat," invigorate blood, and detoxify.¹ The Complete German

¹ Hsu H, Chen C, Shen S, Hsu C, Chen C, Chang S, *Oriental Materia Medica: A Concise Guide*, Keats Publishing, New Canaan, Connecticut, 147-148, 1986.

Commission E Monographs lists knotweed as safe with no known side effects or contraindications.² The American Herbal Products Association (AHPA) has also listed *Polygonum cuspidatum* (knotweed) in their 2nd edition of Herbs of Commerce.³

- b. *trans*-Resveratrol, the principle constituent of *Polygonum cuspidatum* root extract, can be found naturally in the human food supply in grape skins⁴, red and white wine^{5,6} and peanuts^{7,8}.
 - i. *trans*-Resveratrol can be found as a constituent of red wine, white wine and grape juice. Scientists believe the attributes of the “French Paradox” have much to do with the consumption of red wine in which *trans*-resveratrol is a constituent.^{9,10} The concentration of naturally occurring *trans*-resveratrol in red wine ranges from less than 1 to 13.4 milligrams per liter (3.4 mg/250 ml glass).⁵ Consumption of 500 milliliters of grape juice per day enriched with 2 milligrams of *trans*-resveratrol significantly reduced blood platelet aggregation compared to non-enriched grape juice.¹¹ The researchers concluded that *trans*-resveratrol can be absorbed from grape juice in biologically active quantities and in amounts that are likely to promote a healthy cardiovascular system
 - ii. Virginia, runner, and Spanish (peanuts), produced in four different locations contained from 0.03 to 0.14 microg of resveratrol/g. Seed coats from runner and Virginia types contained approximately 0.65 microg/g of *trans*-resveratrol, which is equivalent to <0.04 microg/seed. Quantitative analysis of 15 cultivars representing 3 peanut market types, which had been cold stored for up to 3 years, indicated a range of 0.02-1.79 microg/g of peanut.^{7,8}

² Blumenthal M, Busse W, Goldberg A, Gruenwald J, Hall T, Riggins W, Rister R, The Complete German Commission E Monographs, American Botanical Council, 157-158, 1998.

³ McGuffin M, Kartesz J, Leung A, Tucker A, Herbs of Commerce, American Herbal Products Association 2nd Edition, 117, 2000.

⁴ Soleas GJ, Diamandis EP, Goldberg DM: Resveratrol: a molecule whose time has come? and gone? *Clin Biochem* 30:91-113, 1997.

⁵ Goldberg D, Yan J, Ng E, Diamandis EP, Karumanchiri A, Soleas G, Waterhouse AL, A global survey of *trans*-resveratrol concentrations in commercial wines, *Am J Enol Vitic* 46:159-165, 1996.

⁶ Goldberg D, Ng E, Karumanchiri A, Diamandis EP, Soleas GJ, Resveratrol glucosides are important components of commercial wines, *Am J Enol Vitic*. 47:415-420, 1996.

⁷ Sanders TH, McMichael RW Jr, Hendrix KW. Occurrence of resveratrol in edible peanuts, *J Agric Food Chem* 48:1243-6, 2000.

⁸ Sobolev VS, Cole RJ: *trans*-Resveratrol content in commercial peanuts and peanut products, *J Agric Food Chem* 47:1435-9, 1999.

⁹ Kopp P: Resveratrol, a phytoestrogen found in red wine, a possible explanation for the conundrum of the ‘French paradox’? *Eur J Encrinol* 138:619-620, 1998.

¹⁰ Stanley LL, Mazier MJP: Potential explanation for the French paradox. *Nutr Res* 19:3-15, 1999.

¹¹ Pace-Asciak CR, Rounova O, Hahn SE, Diamandis EP, Goldberg D, Wines and grape juices as modulators of platelet aggregation in healthy human subjects, *Clin Chim Acta* 246:163-182, 1996.

- c. *trans*-Resveratrol has also been the subject of much scientific review. A summary of human studies is presented below. None of the studies reported any toxic events.
- i. Oral administration of a single dose of resveratrol (1.5 mg/kg body weight) to ten healthy human volunteers stimulated the release of plasma adenosine (an endogenous nucleoside) level. Adenosine level increased progressively and reached a peak 30min after ingestion and successfully decreased to the starting values at 120 min. Adenosine is considered one of the mediators, if not the only mediator, of the most important spontaneous organic protection against chronic ischemia, a phenomenon known as “ischemic preconditioning”. This study demonstrates the promotion of a healthy cardiovascular system from the consumption of *trans*-resveratrol.¹²
 - ii. Resveratrol inhibited peroxidation of the LDL cholesterol obtained from two healthy volunteers by 81% and 70% upon the addition of 10 mmol/lit of resveratrol, thereby promoting a healthy heart. In contrast, 10 mmol/lit of α -tocopherol (natural vitamin E), which has been associated with a reduced risk of heart disease, had a much lower antioxidant potency than resveratrol, inhibiting LDL cholesterol oxidation by only 40% and 19%.¹³
 - iii. Resveratrol lowered platelet aggregation of healthy human blood plasma by 50.3% at a concentration of approximately, 3.5 mg/l. Red wine containing 1.2 mg/l of natural *trans*-resveratrol and 3.6 g/l of polyphenols diluted 1000-fold (final resveratrol concentration: 1.2 mg/l) inhibited platelet aggregation by 42%. By adding resveratrol to wine up to a concentration of 1.2 mg/l, inhibition was raised to 78.5%. These results suggest that the antiaggregating activity of resveratrol is related to its concentration in wine, promoting a healthy cardiovascular system.¹⁴ Resveratrol also inhibited ADP- and thrombin-induced platelet aggregation of healthy human blood plasma in a dose-dependent manner (IC₅₀ of 129.9 and 164.7 mmol/l, respectively).¹⁵
5. **Conclusion:** The preceding information demonstrates that 0.5 – 4 mg *trans*-resveratrol (or 1– 8 mg of Protykin®), the recommended daily dose, is a quantity available from various common dietary sources; has a history of consumption from dietary sources; is an amount consistent with that used in scientific research; and is a dose that can reasonably be expected to be safe.

¹² Blardi P, De Lalla A, Volpi L, Di Perri T: Stimulation of endogenous adenosine release by oral administration of quercetin and resveratrol in man. *Drugs Exptl Clin Res* XXV:105-110, 1999.

¹³ Frankel E, Waterhouse AL, Kinsella JE: Inhibition of human LDL oxidation by resveratrol. *Lancet* 341:1103-1104, 1993.

¹⁴ Bertelli AE, Giovannini L, Giannessi D, Migliori M, Bernini W, Fregoni M, Bertelli A: Antiplatelet activity of synthetic and natural resveratrol in red wine. *Int J Tiss Reac* XVII:1-3, 1995.

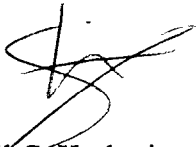
¹⁵ Pace-Asciak CR, Hahn SE, Diamandis EP, Soleas G, Goldberg D, The red wine phenolics *trans*-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease, *Clin Chim Acta* 235:207-219, 1995.

Currently, no claims are being considered for this submission. References used above are to demonstrate safety for human consumption and are not intended as marketing claims. All claims and label copy will be submitted to Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-810).

If more information is required or you should have any questions or comments, please do not hesitate to contact the undersigned.

6. Signature of Manufacturer

Respectfully yours,
InterHealth Nutraceuticals, Inc.

A handwritten signature in black ink, appearing to read 'Shil C. Kothari', with a stylized flourish at the end.

Shil C. Kothari
Product Development Manager

Attachments (17)

- 1 – Product Specification Sheet
- 1 – Certificate of Analysis
- 12 – Literature References



RSV-5000 (Powder)

PRODUCT SPECIFICATIONS

DESCRIPTION

Protykin® RSV-5000 is a high-potency, standardized extract of *Polygonum cuspidatum* (root) containing 50% natural *trans*-resveratrol in powder form for use as a dietary supplement.

SPECIFICATIONS

Chemical Classification	Organic, Nutritive
Physical Classification	Powder, Non Fibrous
Color	Medium Brown
Odor	Characteristic Smokey-Herbal
Taste	Characteristic Bitter-Herbal
Plant Part Used	Root
Moisture	Less than 5%
Solubility (alcohol)	75%
Solubility (water)	None
Clarity (1g/100ml water)	Clear Light Reddish – Brown
pH (1g/100ml water)	5.0 – 7.0
<i>trans</i> -Resveratrol (%) by HPLC	50 ± 5
Emodin (%) by HPLC	Less than 2
Heavy Metals:	
Pb (ppm)	Less than 10
As (ppm)	Less than 10
Hg (ppm)	Less than 0.25
Cd (ppm)	Less than 0.25
Particle Size:	
Wt. % Through 100 Mesh	NLT 75
Microbiological Assays:	
Total Plate Count (CFU/g)	Less than 3000
Yeast and Mold (CFU/g)	Less than 10
<i>E. Coli</i> (CFU/g)	Negative
<i>Salmonella</i> (CFU/g)	Negative
<i>Staph. aureus</i> (CFU/g)	Negative
Shelf Life	2 years when stored in tightly closed containers free of excessive heat, moisture, light and air.

PACKAGING

Protykin RSV-5000 is available in 0.1 (minimum), 0.25, 0.5, 1, 2, 4 and 10 kilogram quantities packaged in moisture, air and light-resistant containers.

Product Code RSV-5000

Research Code IH727

Order Code FG14010

PK1-991115-010103

5451 Industrial Way • Benicia, CA 94510 • (707) 751-2800 • FAX (707) 751-2801





Certificate of Analysis

Product:	Protykin
	RSV-5000
Description:	Extract of <i>Polygonum cuspidatum</i>
Part of Plant:	Root
Control Number:	102004
Date of Production:	March 2001
Shelf Life:	2 Years
Analysis Performed By:	Vendor Lab 1
	Vendor Lab 2

Results of Analysis:

Identification:	Passes
Moisture (%):	1.8
Resveratrol (mg/g):	
trans-Resveratrol (mg/g):	541.8
Heavy Metals as Pb (ppm):	<3
Particle Size:	
Wt% Thru 150 Mesh:	86.9
Microbiological Assays:	
Total Plate Count (CFU/g):	<100
<i>E coli</i> :	Negative
<i>Salmonella</i> :	Negative
Yeast:	<10
Mold:	<10
<i>Staph. aureus</i> :	Negative

Confirmation that specification data from independent laboratory is accurately disclosed on this Certificate of Analysis.

InterHealth Nutraceuticals, Inc.

By:

Date

4/27/2001